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## Prostate Cancer

# Long-term Survival Outcomes for Men Who Provided Ejaculate Specimens for Prostate Cancer Research: Implications for Patient Management

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## Abstract

**Background:** Determining whether men diagnosed with early prostate cancer (PCa) will live long enough to benefit from interventions with curative intent is difficult. Although validated instruments for predicting patient survival are available, these do not have clinical utility so are not used routinely in practice.

**Objective:** To test the hypothesis that volunteers who provided ejaculate specimens had a high survival rate at 10 and 15 yr and beyond.

**Design, setting, and participants:** A total of 290 patients investigated because of high serum prostate-specific antigen donated ejaculate specimens for research between January 1992 and May 2003. The median age at the time of ejaculation was 63.5 yr. 153 of the donors were diagnosed with PCa and followed up to December 31, 2013.

**Outcome measurements and statistical analysis:** Survival outcomes were compared with those for the whole population, as indicated by life expectancy tables up to 20 yr. **Results and limitations:** Men in the PCa group had life expectancies comparable with values listed in life expectancy tables for the whole population. Overall, PCa-specific and relative survival were significantly better for men in the non-PCa and PCa groups in comparison with men diagnosed with PCa in Queensland during the same period. Relative survival for those aged 20–49, 50–64, and ≥65 yr was >100% for ejaculate donors and 81.5%, 82.7%, and 65.2%, respectively, for the Queensland Cancer Registry reference at 10 yr. These findings for this highly selected patient cohort support the hypothesis that an ability to provide an ejaculate specimen is associated with a high likelihood of surviving 10–20 yr after donation, whether or not PCa was detected.

**Conclusion:** Life expectancy tables may serve as a quick and simple life expectancy indicator for biopsy patients who donate ejaculate.

**Patient summary:** Life expectancy tables indicated survival of up to 20 yr for men who provided ejaculate specimens for prostate cancer research.

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## 1. Introduction

Selecting the most appropriate management for men with early prostate cancer (PCa) is beset by many uncertainties [1,2]. Prominent among these is predicting which patients will live long enough to benefit from interventions with curative intent given the long natural history of PCa and the age groups involved. In terms of survival, life expectancy of at least 10 yr is generally accepted as required to justify treatment and therefore testing [3,4].

Published evidence indicates that doctors are less than perfect in estimating survival [5]. In the Prostate Cancer Intervention versus Observation Trial (PIVOT) of radical prostatectomy (RP) and observation for localized PCa, 47.0% randomised to RP died during a median follow-up of 10.0 yr, compared with 49.9% assigned to observation; 5.8% died from PCa or treatment in the RP group compared with 8.4% in the observation arm [6]. In the randomised Swedish trial of RP versus watchful waiting (WW), 57.6% in the RP group and 70% in the WW group had died, 12.4% and 28.4%, respectively, from PCa, during a median follow-up of 13.4 yr [7]. Comparable outcomes have been observed following radiation therapy [8]. Daskivich et al [9] observed from the Surveillance, Epidemiology, and End Results-Medicare database that for 96 032 men aged >66 yr with early-stage PCa (Gleason ≤7) diagnosed during 1991–2007, 52% had life expectancy <10 yr, and nearly half had received aggressive treatment.

Although validated instruments are available for investigating general comorbidity-related deaths [10], none has become established in routine clinical use on a day-to-day basis, reflecting findings from a systematic review that found none of the life expectancy prediction tools available for localised PCa patients is sufficiently adequate to justify implementation into clinical practice [11]. It has recently become apparent that the onset of erectile dysfunction (ED) serves to herald fatal events from cardiovascular disease [12]. One large study reported a median time to death from a cardiovascular cause following the onset of ED to be 10 yr [13] since the reason for ED in the majority of cases is impaired arterial flow [12]. However, assessment of ED through patient histories and validated instruments is problematic because of the unreliability of patient reporting in questionnaires such as the International Index of Erectile Function (IIEF) [14,15].

We have been studying ejaculate as part of our early PCa research studies for many years, and hypothesised that these volunteers, all of whom had been vetted by urologists and were considered for treatment with curative intent should significant PCa be detected, would have a high survival rate, and that the ability to provide an ejaculate specimen would hence serve as a simple indicator of life expectancy. Thus, the aim of this study was to examine the survival outcomes for men who provided ejaculate specimens before 2003 for our research studies.

## 2. Patients and methods

### 2.1. Patients

Between January 1992 and May 2003, men referred to the Urology Unit of the Royal Brisbane and Women's Hospital (RBWH) (93%) or attending

a urologist privately (7%) for investigation of abnormal prostate-specific antigen (PSA) with or without an abnormal digital rectal examination (DRE) were approached to volunteer a specimen of ejaculate for our research into early diagnosis of PCa. All were booked to have a diagnostic transrectal ultrasound (TRUS)-guided biopsy. Ejaculate specimens were provided before or 1 mo after biopsy.

### 2.2. Histology and PSA

Histologic diagnoses were obtained from the Queensland Cancer Registry and cross-checked with Queensland Health databases, institutional research files, and the files of relevant private pathology laboratories. Serum PSA levels before ejaculate donation and biopsy procedures were also obtained by interrogating the databases of Queensland Health and private Queensland pathology laboratories.

### 2.3. Patient outcomes

Dates and causes of death were obtained from the Queensland Health Hospital Business Corporate Information Services programme, Queensland Cancer Registry, patient hospital notes, relevant research databases, and private doctors' records, and were confirmed via the National Death Index.

### 2.4. Ethical approval

Human research ethics approval was given by the University of Queensland (project no. 2006000262) and from RBWH ethics committees (94/29; 1995/088B) with access to the Queensland Cancer Registry data approved by Queensland Health.

### 2.5. Measures

The cohort was stratified into three groups (biopsy positive, biopsy negative, and no biopsy performed) according to their biopsy status for PCa. PSA before ejaculate donation (<4 ng/ml, 4–10 ng/ml, and >10 ng/ml) and patient age at the time of ejaculation (modelled as a continuous variable but reported in categories of <50 yr, 50–65 yr, and >65 yr) were considered in the analyses and compared with Queensland population 10-yr survival data for PCa diagnoses during 1993–2003.

### 2.6. Statistical analysis

Survival times were taken from the date of ejaculate donation to the date of death or December 31, 2013, whichever came first. Men not known to have died by December 31, 2013 were considered alive, and therefore censored in the survival analysis. Median potential follow-up time was calculated using the reverse Kaplan-Meier method [16].

Our primary outcome of interest was all-cause survival. Kaplan-Meier survival curves were generated for the total cohort and stratified by biopsy status, PSA before ejaculate donation, and age group at the time of ejaculation.

In the absence of comparative data for men who did not provide ejaculate specimens during the study period, we used total population and cancer registry data as the comparison groups. Differences observed using this methodology are thus likely to be biased toward the null compared with the true value. We used relative survival to compare all-cause survival outcomes among the cohort with that for the age- and sex-matched population. The Ederer II method [17] was used to calculate expected survival.

While previous studies have used generalised linear models with a Poisson error structure to model excess mortality, convergence issues when the cohort mortality is less than for the general population [18] necessitated comparison of relative survival estimates for subgroups

**Table 1 – Cohort characteristics by cancer group and 10-yr all-cause survival**

	Total cohort		No prostate cancer found		Prostate cancer	
	<i>n</i>	10-yr survival, % (95% CI)	<i>n</i>	10-yr survival, % (95% CI)	<i>n</i>	10-yr survival, % (95% CI)
Cohort	290	83.5 (79–87)	137	89.1 (83–93)	153	78.4 (71–84)
Age at ejaculate donation						
20–49 yr	25	100.0	19	100.0	6	100.0
50–65 yr	151	91.4 (86–95)	74	94.6 (86–98)	77	88.3 (78–94)
>65 yr	113	69.0 (60–77)	44	75.0 (59–85)	69	65.2 (53–75)
Unknown	1		0		1	
PSA value						
<4.0 ng/ml	80	88.8 (80–94)	51	90.2 (78–96)	29	86.2 (67–96)
4.0–10 ng/ml	95	87.4 (79–93)	44	88.6 (75–95)	51	86.3 (73–93)
>10 ng/ml	87	70.1 (59–79)	27	85.2 (65–94)	60	63.3 (50–74)
No PSA	28	96.4 (77–99)	15	93.3 (61–99)	13	100.0
Follow-up						
<5 yr	20	Not applicable	6	Not applicable	14	Not applicable
5–9 yr	28		9		19	
10–14 yr	80		24		56	
≥15 yr	162		98		64	

CI = confidence interval.

using 95% confidence intervals (CIs) rather than a formal statistical test. When the 95% CI for a relative survival estimate did not include one, survival in this group was considered significantly different to that of the general population.

For all-cause survival, flexible parametric survival models [19,20] were used to examine the impact of covariates. Flexible parametric survival models were fitted on the log cumulative hazard scale [19,20] with natural cubic splines to estimate the baseline log cumulative excess hazard function. We used the hazard scale with four degrees of freedom, with a forward selection process to determine the time dependence of any regression coefficients [19]. We plotted average predicted subgroup-specific survival estimates from the flexible parametric model with the observed Kaplan-Meier survival estimates for that subgroup, and tabulated predicted 20-yr survival probabilities with 95% CIs for specific combinations of the covariates. Age was modelled as a continuous variable with incorporation of a smooth rank transform [20].

### 3. Results

A total of 290 eligible men provided specimens at a median age of 63.5 yr (Table 1). The median follow-up was 16.9, 16.1, and 17.3 yr for the total, PCa, and no-PCa cohorts respectively. The median follow-up was 10.7 yr (1.0–19.0 yr) for the 103 men who died from any cause from the date of ejaculate donation and 16.6 yr (10.9–20.5 yr) for those still alive at the time of data review. A biopsy-confirmed diagnosis of PCa was made for 153 patients; 137 did not have PCa detected, but 37 of these men elected not to proceed to biopsy. The majority of men were aged 50–65 yr at the time of ejaculate donation (Table 1), with 113 (39.1%) >65 yr. PSA measurement was obtained for 90% of the cohort, with values similarly split between the <4 ng/ml, 4–10 ng/ml, and >10 ng/ml categories.

Of the 103 men known to have died during the study period, 15 were certified as having died of cardiovascular disease, 27 from other cancers (Table 2), 29 from PCa, and 20 of other causes; for the remaining 12 who died, no information about the cause of death was available.

#### 3.1. All-cause survival

All-cause Kaplan-Meier survival estimates (Table 3, Fig. 1) demonstrate better survival outcomes experienced by men with no PCa (79% survival after 15 yr) than men diagnosed with PCa (57.8% survival after 15 yr).

Visual comparisons between the subgroup-specific Kaplan-Meier all-cause survival estimates and modelled survival curves (Fig. 2) show strong agreement, suggesting an appropriate fit of the survival model.

From the multivariate survival model, adjusted survival probability (all causes) decreased as age increased (Table 5, Fig. 2) and PSA levels increased, and was higher for men without a cancer diagnosis.

#### 3.2. Comparisons with the general population (relative survival)

Examination of relative survival estimates (Table 4 and Fig. 3) showed that the relative survival for men who had no

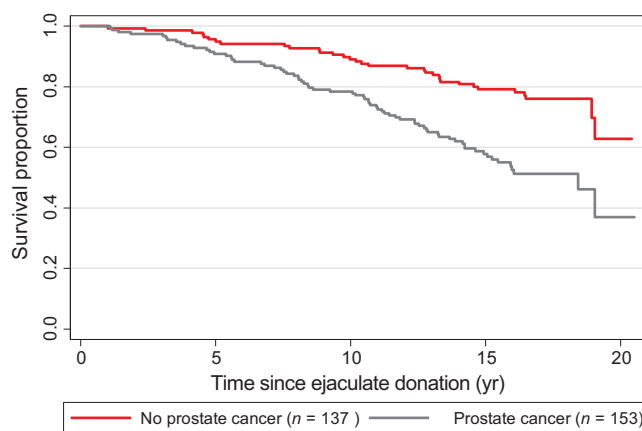
**Table 2 – Cancer causes of death other than prostate cancer**

Cancer causing death	No prostate cancer		Prostate cancer ( <i>n</i> = 153)
	Biopsy ( <i>n</i> = 100)	No biopsy ( <i>n</i> = 37)	
Lung	5	1	2
Colorectal		1	3
Brain		1	1
Pancreas	1		2
Lymphoma	1	1	2
Bladder	1		
Renal		1	
Oesophageal	1		
Melanoma	1		
Cholangiocarcinoma			1
Gastric			1
Total	10	5	12

**Table 3 – All-cause survival observed and median age at ejaculate donation**

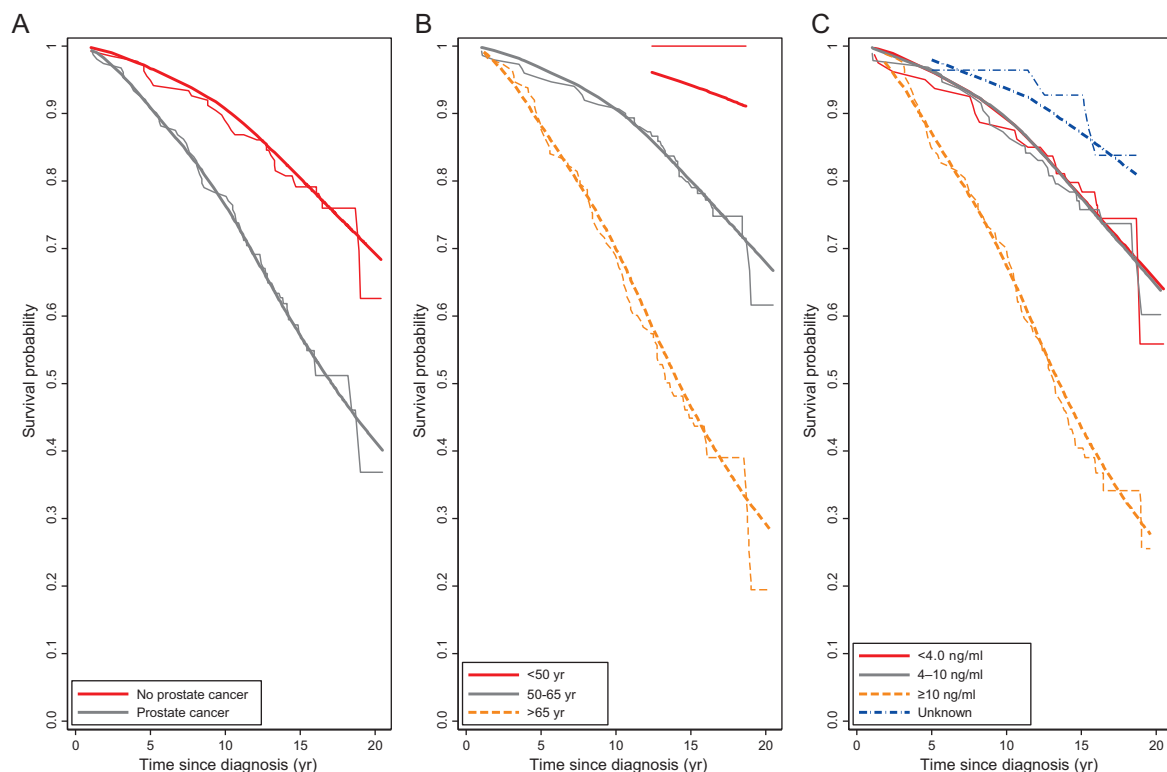
Follow-up	All participants (n = 290)		No prostate cancer (n = 137)		Prostate cancer (n = 153)	
	Median age, yr (n)	Survival, %, (95% CI)	Median age, yr (n)	Survival, %, (95% CI)	Median age, yr (n)	Survival, %, (95% CI)
5 yr	63 (269)	93.1 (90–95)	61 (131)	95.6 (91–98)	65 (138)	90.1 (85–94)
10 yr	62 (241)	83.5 (79–87)	61 (122)	89.1 (83–93)	64 (119)	78.4 (71–84)
15 yr	61 (161)	68.1 (62–73)	59 (98)	79.2 (71–85)	63 (63)	57.8 (49–65)
20 yr	63 (3)	50.0 (37–62)	65 (2)	62.7 (42–78)	63 (1)	36.9 (19–55)

CI = confidence interval.  
Note that the group with no prostate cancer includes 37 participants who did not proceed to biopsy.

**Fig. 1 – Kaplan-Meier all-cause survival estimates by diagnostic group.**

cancer diagnosis increased with time since ejaculate donation. These men had a substantially better survival outcome (or negative excess mortality) than the age-matched male general population at 10 yr or more after ejaculate donation, with many of the lower limits of the 95% CIs in Figure 3 not including 100%. By contrast, relative survival for men diagnosed with PCa tended to decrease across the follow-up interval, while they continued to have equivalent mortality expectations to those of the general population, since the CIs included 100%.

Tables 6 and 7 detail 10-yr survival findings for the study cohort and the Queensland male population. Overall, PCa-specific and relative survival were significantly better for the study cohort than for the whole of Queensland, with findings most pronounced for those aged  $\geq 65$  yr.

**Fig. 2 – Modelled (flexible parametric model, thick lines) and observed (Kaplan-Meier, thin lines) all-cause survival by cohort subgroup: (A) diagnostic group, (B) age at ejaculate donation, and (C) prostate-specific antigen level.**

**Table 4 – Relative survival observed**

Follow up	Relative survival, % (95% confidence interval)		
	All participants (n = 290)	No prostate cancer (n = 137)	Prostate cancer (n = 153)
0–5 yr	102.0 (98–105)	103.0 (97–106)	101.1 (95–105)
5–10 yr	103.1 (97–108)	105.7 (98–111)	100.6 (91–108)
10–15 yr	98.0 (90–114)	106.7 (96–115)	88.3 (75–100)
15–20 yr	104.6 (90–114)	115.2 (99–128)	88.0 (68–107)

Note that the group with no prostate cancer includes 37 participants who did not proceed to biopsy.

**Table 5 – Adjusted 10-yr all-cause survival estimates from the full model for the total cohort (n = 290)**

	Survival (%)	95% CI (%)
Age at ejaculate donation <sup>a</sup>		
20–49 yr	97.5	96–99
50–65 yr	90.7	88–94
>65 yr	69.8	64–77
PSA value		
<4.0 ng/ml	89.2	85–94
4.0–10 ng/ml	89.3	85–94
>10 ng/ml	67.3	60–75
No PSA	94.1	89–100
Diagnostic group		
No prostate cancer	90.6	87–94
Prostate cancer	76.3	71–82

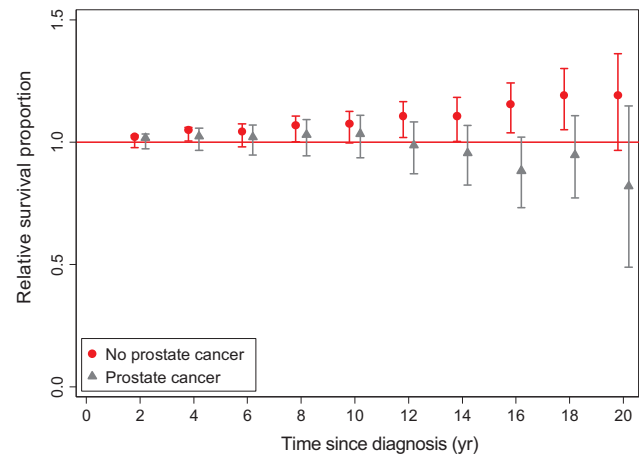
CI = confidence interval.  
<sup>a</sup> Age at ejaculate donation was modelled as a transformed continuous variable, and then predicted survival probabilities were collapsed over these groups.

**Table 6 – Survival at 10 yr for men included in the ejaculate cohort and diagnosed with prostate cancer (PCa) according to age at ejaculate donation**

Age group	Survival (%)		
	Overall	PCa-specific	Relative
20–49 yr	100	100	103.0
50–64 yr	88.3	92.0	100.2
≥65 yr	65.2	86.2	100.2
All ages combined	78.4	90.1	100.6

#### 4. Discussion

Survival results for participants, all of whom provided an ejaculate specimen at least 10 yr (and up to 21 yr) before the

**Fig. 3 – Relative survival estimates by diagnostic group.**

cut-off time for analysis (December 31, 2013), strongly support the hypothesis that volunteers who provided ejaculate specimens for our research studies had a high survival rate at 10, 15, and 20 yr. Overall, PCa-specific and relative survival findings were significantly better for all age groups in favour of the study cohort, and were most pronounced in those aged ≥65 yr. In addition, we found a close survival correlation with men of the same age as indicated by life expectancy tables for Queensland males for those diagnosed with PCa, raising the prospect that this ready reference could serve as a simple indicator of life expectancy. For those in whom PCa was not detected, survival prospects to 20 yr increasingly exceeded those of their age-matched contemporaries in the general population.

Having detailed information for an overall median follow-up of 15.6 yr, with 10.4 yr for those who died and 16.6 yr for those still alive at 10.9–20.5 yr after they provided their ejaculate specimen, allowed us to determine more than just projected outcomes via Kaplan-Meier estimates. In addition to actual overall data, we could estimate relative survival. We believe that relative survival is much more clinically relevant as it permits direct comparison of an individual's survival data with peer data as recorded in population life expectancy tables, since placing survival prospects in the context of age norms is most relevant in judging clinical applicability, particularly for patients aged ≥65 yr. However, predicting outcome at an

**Table 7 – Survival at 10 yr for men diagnosed with prostate cancer (PCa) in Queensland between 1993 and 2003 according to the Queensland cancer registry**

Age at diagnosis	Diagnoses (n)	Deaths within 10 yr of diagnosis (n) <sup>a</sup>			Alive 10 yr after diagnosis (n)	Survival, % (95% confidence interval)		
		PCa	Other cancers	Non-cancer		Overall	PCa-specific	Relative
20–49 yr	213	40	<10	<10	163	77.2 (71–82)	81.5 (76–86)	79.3 (73–85)
50–64 yr	4999	821	240–250	280–290	3655	73.1 (72–74)	82.7 (82–84)	81.7 (80–83)
≥65 yr	16 511	4,247	1424	4749	6091	37.5 (37–38)	68.4 (68–69)	65.2 (64–67)
Total	21 723	5,108	1670	5036	9909	46.1 (45–47)	72.4 (72–73)	70.1 (69–71)

<sup>a</sup> Some data are presented as a range rather than a specific value because of low numbers.



individual level needs to be tempered by cancer status, particularly for those who developed other cancers [21], none of whom survived to 20 yr following specimen donation, reflecting the shorter natural histories of these other malignancies.

The reasons for not proceeding to biopsy for the 37 men who had a serum PSA test as part of their investigation for PCa and were referred for urological assessment are not known for all patients. As a result of ad hoc conversations, it became evident that a number did not proceed because they reassessed their level of risk and concluded that the likelihood of a positive cancer biopsy was reduced and the risks associated with biopsy were not warranted. We were unable to confirm whether some of these donors had biopsies elsewhere.

The need for better diagnostic tests for PCa is undisputed. We consider that sampling cells and fluid from prostatic acini is the best noninvasive method for collecting specimens to study, but these have not been easy to obtain for a number of reasons that include increased costs for donors and community mores. ED is increasingly a problem as men age [22]. The median age of contributors was 63.5 yr, with 38.9% (113/290) older than 65 yr, which is surprising given the expected reticence for this age group towards a request to provide an ejaculate specimen during 1993–2003. Patients younger than 50 yr constituted only 8.6% of the donor population.

All participants were members of a highly selected group. Ordinarily, this would lessen the value of the study. However, with the ongoing need to identify at-risk men who will live long enough to benefit from diagnosis and treatment of PCa should it be detected, these findings are particularly relevant and reassuring. According to the premise that the ejaculate donor cohort represented men with favourable survival prospects beyond erectile competence, which by inference includes good cardiovascular status [12,13], we suspect that their survival outcomes would be superior compared to a cohort selected purely on the basis of IIEF or Sexual Health Inventory for Men scores. However, this contention can only be settled conclusively in a prospective trial.

It is unknown whether participants in this study used erection aids. Phosphodiesterase inhibitors only became available in Australia in 1998 for the first time, with the costs of purchase expected to have been beyond the reach of most of the donors. The large majority of the participants were public patients (93%), a population group recognised to have poorer outcomes for both overall and cancer survival as a consequence of lower socioeconomic status [23–25].

Accurate determination of cause of death and separation of those who died into categories on the basis of death certificates are always problematic. There are differences between individual assessors attributing cause of death [26] and often marked differences between death certificates and autopsy findings [27]. By comparing survival between individuals not diagnosed with PCa and individuals who were, we avoid this problem.

Although ability to produce an ejaculate specimen does not always reflect normal erectile capability, it is

improbable that those who volunteered and donated specimens on demand had significant ED. Furthermore, willingness to provide and then donate an ejaculate specimen for research is much more than an indicator of whether or not ED and, by inference, underlying cardiovascular morbidity are present, so such donation may bring new meaning to the term performance index, possibly extending the independent prognostic significance of high Eastern Cooperative Oncology Group scores and Karnovsky index ratings in clinical trials.

## 5. Conclusions

In conclusion, the study results strongly support the hypothesis that volunteers who provided ejaculate specimens for our research studies have a high survival rate. Furthermore, they indicate that life expectancy tables may serve as a ready reference to indicate probable survival for ejaculate donors diagnosed with PCa, especially for those aged >65 yr.

**Author contributions:** Robert A. Gardiner had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Gardiner, Baade, Williams.

*Acquisition of data:* Ashrafi, Baade, Gardiner.

*Analysis and interpretation of data:* Baade, Gardiner, Ashrafi, Williams.

*Drafting of the manuscript:* Gardiner, Baade, Williams, Roberts.

*Critical revision of the manuscript for important intellectual content:* All authors.

*Statistical analysis:* Baade, Williams, Ashrafi.

*Obtaining funding:* Gardiner.

*Administrative, technical, or material support:* Ashrafi, Roberts.

*Supervision:* Gardiner, Baade.

*Patient accrual:* Gardiner, Yaxley.

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